

Review

Towards a Unified View on Pathways and Functions of Neural Recurrent Processing

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There are three neural feedback pathways to the primary visual cortex (V1): corticocortical, pulvinocortical, and cholinergic. What are the respective functions of these three projections? Possible functions range from contextual modulation of stimulus processing and feedback of high-level information to predictive processing (PP). How are these functions subserved by different pathways and can they be integrated into an overarching theoretical framework? We propose that corticocortical and pulvinocortical connections are involved in all three functions, whereas the role of cholinergic projections is limited by their slow response to stimuli. PP provides a broad explanatory framework under which stimulus-context modulation and high-level processing are subsumed, involving multiple feedback pathways that provide mechanisms for inferring and interpreting what sensory inputs are about.

Recurrent Feedback to Primary Sensory Areas

Primary sensory cortical areas are the entry points for sensory information reaching the cortex. Sensory information arrives through thalamic projections, and after processing in primary areas information is forwarded to higher sensory and association cortices. In addition to engaging in feedforward processing [1], primary sensory cortices receive feedback from higher cortical areas and thus partake in **recurrent processing (RP)** (see **Glossary**) [2,3], which may serve multiple functions (**Figure 1**). Feedback reaches the primary sensory cortices through various anatomical pathways. Here we focus mainly on V1 and highlight three major pathways that have been identified in both primates and rodents (**Figure 2** and **Box 1**). First, V1 receives reciprocal feedback projections from those visual cortices that it projects to, most notably areas V2, V3, and V4 [2] in primates and the **lateromedial (LM)** and **posteromedial (PM) cortices** in rodents [4,5], which we call short-range projections. Additionally, V1 receives input from higher cortical areas in the temporal, parietal, and frontal lobes [2]. These higher areas project to V1 along the same hierarchical routes (e.g., via V4 in primates [6]) and in mice also through direct long-range projections [7]. Second, in the context of thalamic pathways, V1 receives not only feedforward projections from the lateral geniculate thalamic nucleus (LGN) but also feedback from the thalamic **pulvinar** region [8] [or its rodent homolog, the **lateral posterior thalamic nucleus (LP)**] [9]. Because the pulvinar receives projections from visual areas, higher cortical areas and subcortical structures including the amygdala and basal ganglia, its projections to V1 could convey a wide range of information, from stimulus context to cognitive content. Furthermore, pulvinar activity affects the processing of visual information in V1 [10] and V4 [11]. Third, V1 receives neuromodulatory projections from subcortical structures. A feedback loop that is based on V1 and includes any neuromodulatory cell group would involve subloops with many other areas, such as the frontal cortex. Arguably, such a complex loop verges on the definition of recurrent feedback. Because neuromodulators are increasingly regarded as factors influencing sensory and cognitive processing throughout lower cortical and associational areas [12–14], we include some of these projections in this review. Due to space restrictions, we focus on cholinergic projections from the basal forebrain whose role in the modulation of visual processing is becoming

Highlights

Corticocortical feedback to V1 is likely to be involved in contextual modulation of stimulus processing, high-level information processing, and predictive processing.

The pulvinar is proposed to act as a fast, short-cut connection between visual areas to accelerate predictive processing.

Cholinergic projections could contribute to functions of recurrent processing, but the speed of recurrent processing from V1 to the basal forebrain and back is too low to modulate information processing at short latencies.

A plausible anatomical mapping is proposed from a functional model of predictive processing onto cortical microcircuitry.

Stimulus-context modulation and high-level information processing can be encapsulated in a predictive processing framework including feedforward and recurrent processing, if this is broadened to include the generation of interpretations and inferences on sensory inputs in general.

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increasingly clear (e.g., [15]). This does not mean that other neuromodulators such as noradrenaline and serotonin are less interesting or relevant, and we refer the readers to excellent prior reviews on the contributions of some of these pathways to visual processing [12].

What functions does RP serve and through which anatomical pathways are these achieved? We highlight three main functions that have been proposed: (i) contextual modulation of stimulus processing; (ii) feedback of **high-level information**; and (iii) **PP** (Figure 1). We discuss the evidence for their dependence on RP (Table 1) and review specific criteria that need to be met for each proposed function to be mediated by recurrent feedback. Many studies have focused on stimulus-context and high-level feedback to V1 and their outcomes deliver a framework in which we discuss how RP may enable PP. Finally, we explore to what extent the three proposed functions can be integrated under an overarching functional interpretation and we discuss possible connections between RP and (conscious) perception.

Contextual Modulation of Stimulus Processing

Feedback from higher cortical areas reports to the primary sensory areas a wealth of sensory information in which feedforward input is embedded. We illustrate this principle with two examples. A basic form of modulation by the sensory context around a specific visual stimulus is size tuning or surround suppression and the strongly related effect of end stopping. Responses of a V1 neuron to a small visual stimulus that matches the neuron's **classical receptive field** decrease when stimulus size is extended to cover the extrareceptive field, a phenomenon referred to as surround suppression [16,17]. Thus, a V1 neuron is tuned to a preferred stimulus size, which is large enough to cover most of its receptive field but does not extend far outside it. Silencing areas V2 and V3 reduces surround suppression in primate V1 [18], which indicates a role for RP. However, do these areas affect V1 directly through corticocortical projections or via the pulvinar or basal forebrain? Optogenetic inactivation of axonal projections of V2 neurons in V1 reduces surround suppression [19], providing evidence for the involvement of direct corticocortical feedback projections in primates.

A more complex form of surround interaction is figure-ground segregation. Through this process, objects come to be perceived as separate from their background [20]. In the primate V1, figure enhancement of firing rate occurs rapidly (~85–100 ms) [21,22] while background suppression occurs later (~150 ms) [21]. Local field potential recordings across cortical layers in the primate V1 reveal that figure-ground segregation correlates with excitatory inputs reaching layers 1, 2, and 5 [22], which are target layers for cortical but not pulvinar projections, suggesting a contribution of the former but not the latter.

Deployment of corticocortical versus pulvinocortical feedback projections in contextual modulation can be further validated by examining the properties of their synaptic boutons onto V1 neurons. In mice, receptive fields of corticocortical projections from the LM cortex and pulvinocortical projections from the LP onto layer 1 of the V1 match, retinotopically, those of the target V1 neurons [9,23]. The receptive fields of these projections are larger than those of V1 neurons, which means that both can provide input regarding stimulus context to V1 neurons. In some cases, figure-ground segregation can be based on the orientation of the figure versus the background [20,24]. In mice, the majority of LP projections to V1 are not orientation selective [9], in contrast to LM projections, of which approximately half are orientation tuned [23]. This means that, at least in some circumstances, corticocortical projections are better equipped for **stimulus-context modulation** than pulvinar projections. However, given the large receptive fields of pulvinar neurons, and the retinotopy of their projections to V1, the pulvinar could nonetheless make an orientation-independent contribution to stimulus-context modulation [9].

Glossary

Classical receptive field: specific part of the external visual field from which a V1 neuron receives feedforward input.

Generative model: an unsupervised learning approach that captures the statistical regularities in the data and can be used to infer alternative representations of observations. These models are usually described in terms of a joint distribution over the observations, distributed in a high-dimensional space, and their representations. The aim of the models is to learn the underlying distribution generating the data without focusing on specific problems like classification. An example of a generative model is the class of generative adversarial networks (GANs), which are able to produce novel, fictive exemplars from a known distribution of data [118].

High-level information: subjective information regarding the stimulus and its context, such as attentional, motivational, and emotional value, mnemonic information, and semantic interpretation.

Lateral posterior thalamic nucleus (LP): mouse homolog of the pulvinar.

Lateromedial (LM) cortex: a secondary visual cortical area located laterally from V1 in mice.

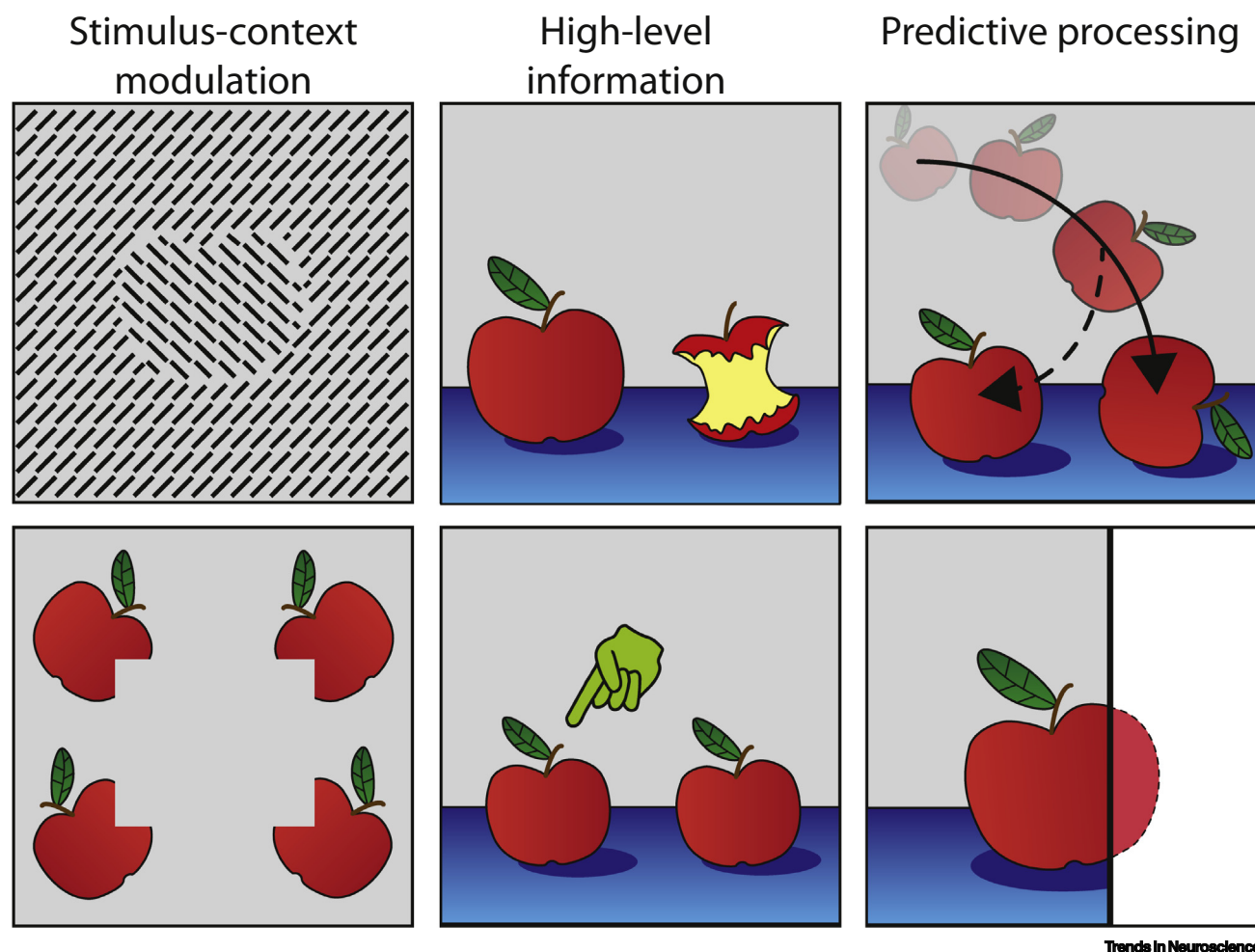
Posteromedial (PM) cortex: a secondary visual cortical area located medially from V1 in mice.

Predictive processing (PP): learning to build inferential representations of the causes of sensory inputs. This type of processing is based on the use of errors between sensory inputs and predictions of these inputs.

Pulvinar: a group of nuclei located posteriorly in the thalamus of primates. The pulvinar receives projections from many cortical and subcortical areas and is strongly interconnected with the visual cortex.

Recurrent processing (RP): interplay of neural activity between two (or more) brain areas, which arises through direct and indirect reciprocal projections in a network of areas connected by one or more loops. In a hierarchical network, this entails feedforward and feedback connections between lower and higher areas.

Stimulus-context modulation: modulation of the response of a neuron to a stimulus within its receptive field, by stimulus features from outside its receptive field.



Trends in Neurosciences

Figure 1. Proposed Functions Related to Recurrent Processing. During stimulus-context modulation (left panels), primary visual cortex (V1) neurons receive information regarding visual features outside their classical receptive field. Top left: The different bar orientations draw out a figure against a background. Bottom left: Cut outs in the apples create illusory contours that form a Kanizsa figure. High-level information (middle panels) constitutes nonsensory, subjective information regarding the (visual) scene that is not captured by a single neuron's receptive field. For example, the full apple in the top-middle figure has a higher subjective value to a hungry person than the apple core. High-level information also includes, for instance, top-down attention effects, as indicated by the pointing hand in the bottom figure. In predictive processing (right panels), feedforward input is compared with predictions from higher cortical areas that are projected back to V1. For instance, the apple falling towards the table evokes predictions regarding the trajectory and impact position on the table. If this prediction fails, and the apple suddenly appears at an unexpected location (left side), the mismatch between feedforward input and feedback prediction results in an error signal. Predictive processing can also be applied in a spatial context (bottom right); for instance, local Gestalt features can predict how visual features are laid out in space, even at an occluded and unseen part of the visual field.

Do cholinergic projections contribute to stimulus-context modulation? In humans, increasing acetylcholine (ACh) levels through systemic drug application attenuates the spatial spread of visual responses as measured using functional magnetic resonance imaging (fMRI) [25] and reduces perceptual surround suppression [26]. Local iontophoretic ACh application in macaques reduces the preferred length of bar stimuli of V1 neurons [27]. These studies indicate that ACh affects stimulus-context processing but they lack specificity regarding the precise origin of this modulation; that is, whether it acts through information regarding visual content within the extrareceptive field, by influencing other feedback projections, or by modulating lateral and/or feedforward processing within V1. Furthermore, a cholinergic feedback loop involves a long pathway, which begs the question: can a cholinergic route respond quickly to

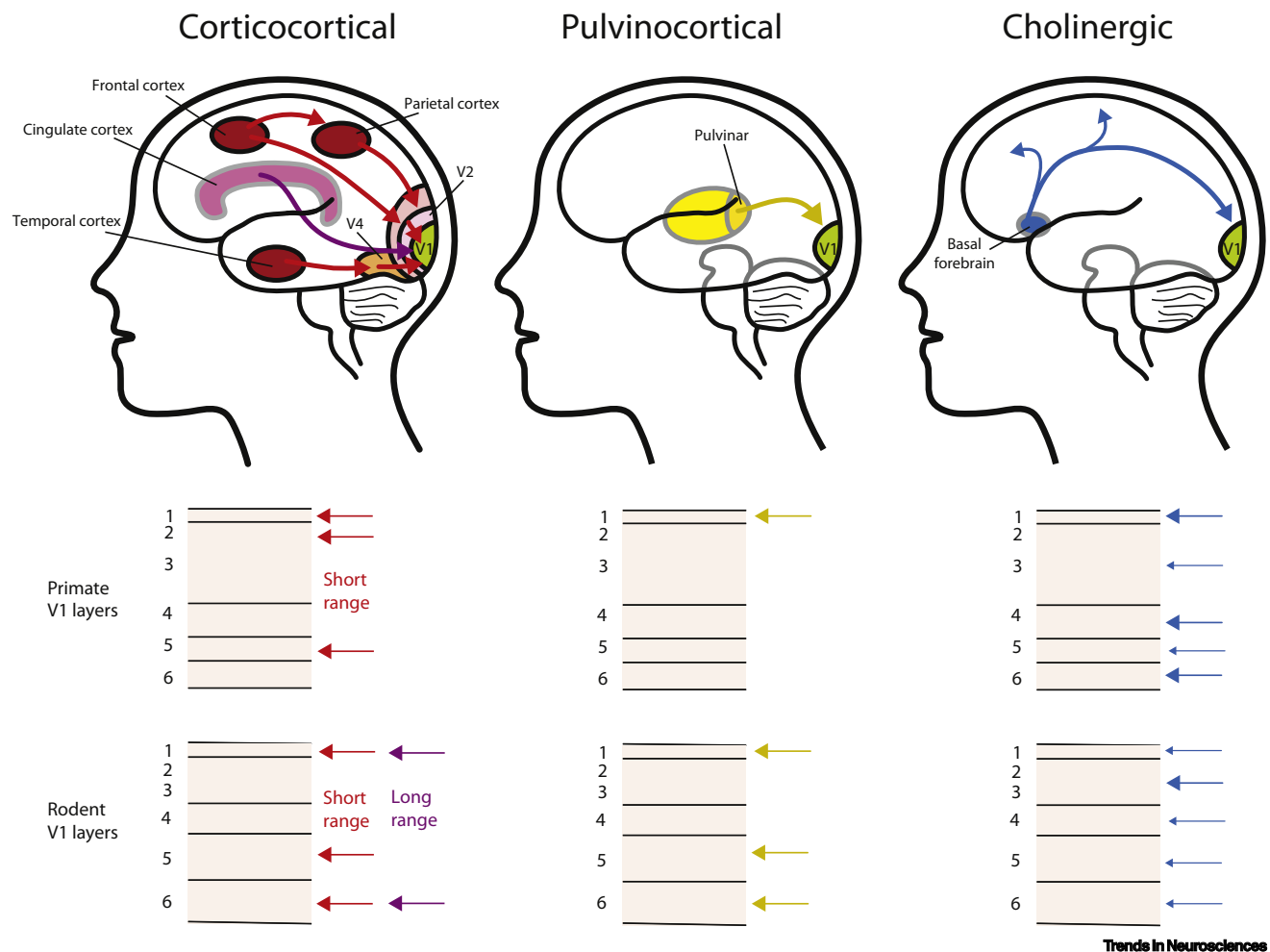


Figure 2. Feedback Projections to V1. Top: Schematics of the anatomy of corticocortical, pulvinocortical, and cholinergic projections to V1; see also [Box 1](#). Bottom: Recurrent projections from these three routes target specific cortical layers in V1 of primates and rodents. The relative sizes of the cortical layers are based on [\[81,82\]](#).

fast-changing stimulus context? Optogenetic activation of the basal forebrain induces an activity change in the mouse V1 relatively fast (i.e., with a 120-ms latency [\[15\]](#)), but one must also consider how fast the basal forebrain reacts to visual input. Basal forebrain neurons in monkeys have an average response latency of between 100 and 490 ms after visual onset [\[28\]](#), which means that this pathway is too slow to contribute to fast stimulus-context modulations such as surround suppression. This agrees with the effects of iontophoretically applied ACh, which affects specifically the late phase (150–280 ms) of stimulus-context modulation [\[27\]](#), including the late phase of figure-ground segregation. Interestingly, this late phase appears to be related to perception (see below).

In summary, corticocortical projections constitute the main mechanism mediating stimulus-context modulation in V1. By contrast, pulvinar projections appear to contribute to aspects of surround modulation that do not require feature-specific feedback (e.g., orientation). Cholinergic projections prove to be too slow to contribute to fast stimulus-context effects but can modulate the late phase of visual processing.

Box 1. Feedback Pathways

Corticocortical feedback projections can target V1 from frontal, temporal, or parietal cortical areas; further, they can target V1 either directly or via several steps throughout the cortical hierarchy. In primates, short-range projections from V2 target mainly layers 1, 2, and 5 and only sporadically layer 3 [83,84]. In mice, however, projections from secondary visual cortices target layer 1 strongly and layers 5 and 6 moderately, but layers 2–4 weakly [5]. The axonal projections to layer 1 of V1 are arranged retinotopically, overlapping with the receptive fields of V1 neurons [23]. Long-range projections from the cingulate cortex to V1 mainly target layers 1 and 6 in mice [7], but long-range projections in primates (e.g., from the parietal cortex) have been reported to be very sparse [85].

The thalamus sends feedforward projections to V1 through the LGN but also sends pulvinocortical feedback relaying information from higher cortical areas (and other brain regions; e.g., superior colliculus, basal ganglia, amygdala) to V1 [86]. These thalamic feedback projections arise from the pulvinar in primates or the LP in rodents [9]. In primates, the pulvinar projects mainly to layer 1 of V1 [8]. In mice, the LP projects mostly to layer 1 but also to deep layers [9]. These projections show a retinotopic distribution [9].

Most cholinergic projections from the basal forebrain collateralize and target multiple areas but can be selective between sensory cortices (e.g., targeting the auditory but not the somatosensory cortex) [87,88]. Cholinergic innervation is found across all layers in V1 but is most dense in layers 1, 4, and 6 in macaques [89]. In mice, cholinergic axons from the basal forebrain to V1 can be found across all layers but are most dense in layers 2/3 [87]. In deep layers, these cholinergic terminals contact only inhibitory, and not excitatory, neurons through direct synaptic contacts [90], but these results need to be validated for other layers. Besides such fast synaptic communication, volume transmission may be a common mechanism in cholinergic communication. Cholinergic receptors can be divided into muscarinic and nicotinic groups, which have differing prevalence across cortical layers and can be found on inhibitory as well as excitatory neurons. Thus, basal forebrain projections can engage a diversity of mechanisms, which is a theme outside the scope of this review and for which we refer to other reviews (e.g., [91]).

Feedback of High-Level Information

High-level information such as value-related [29–31], attentional [29,32–34], and decision-related [35] signals modulates the activity of primary sensory neurons that represent the spatial location or other sensory features of objects, particularly when the objects have acquired motivational significance; for instance, through learning [36]. This modulatory activity is often observed as stronger activity of neurons whose receptive field is susceptible to an object of relevance compared with neurons with receptive fields exposed to irrelevant objects. The full range of high-level information that is projected back to V1 is too wide to discuss here. Different types of high-level information arise from a strongly interconnected set of structures, most notably within the prefrontal and cingulate cortices and their receptive basal ganglia counterparts. Thus, they might all target V1 through the same pathway, be it corticocortical, pulvinocortical, and/or cholinergic. Speaking in favor of this is the finding that spatial attention and reward expectancy modulate V1 activity as a unified selection signal in monkeys [29]. In this section we mainly focus on (spatial) attention.

Which projections convey high-level information to V1? Laminar recordings in the cortex of macaques performing a visual curve-tracing task revealed that attentional modulation targets V1 through superficial layers and layer 5 [37], which concurs with corticocortical, but not pulvinocortical, target layers (in contrast to rodents; Figure 2 and Box 1). Because axonal projections from V2 can increase neural activity within V1 [19], a corticocortical mechanism from higher regions projecting back to V1 through V2 may underlie the increased V1 activity related to attentional feedback, but also leaves room for contributions by other pathways. Single-unit recordings show that pulvinar neurons can be modulated by top-down attention, and pharmacological silencing of this structure interferes with a monkey's performance in an attention task [11,38]. Neuronal activity further suggests that the pulvinar contributes to attention by regulating synchronous firing between multiple areas [39]. In mice, pulvinocortical connectivity maps match with connectivity strength between visual cortical areas, which further indicates a role for the pulvinar in facilitating intercortical communication [40]. The pulvinar could mediate high-level modulation of V1 through its direct connections to V1, via higher visual cortices projecting to V1, or by changing

Table 1. Empirical Findings Related to the Three Types of Feedback Projection and the Three Functions of RP that Are Discussed in this Review^a

	Stimulus context	High-level information	PP
Corticocortical	(+) Optogenetic silencing of V2 projections to V1 reduces stimulus-context modulation in primates [19] (+) In mice, projections from LM to V1 represent visual information exceeding V1 receptive fields and many projections are orientation and direction specific [23]	(+) Laminar profile of attentional modulation in primate V1 matches a corticocortical projection profile [37]	(+) In mice, A2b/M2 projections convey motor information to V1 [52], which is crucial to elicit prediction errors in V1 [52,53] (+) In mice, LM feedback to V1 extends around retinotopically matched locations; this extension is more prominent in a direction orthogonal to the LM neuron's preferred orientations; this suggests that LM neurons suppress predictive representations in V1 [23]
Pulvinocortical	(+/-) In mice, receptive field size and retinotopic overlap of pulvinocortical projections to V1 suggest a role during stimulus-context processing, but low orientation selectivity limits the extent of stimulus-context modulation that may occur [9]	(+) Pulvinar can be modulated by top-down attention and pharmacological silencing of this structure interferes with monkey performance in an attention task [38]; it remains unclear, however, whether this can be attributed to pulvinar-to-V1 connections	(+) In mice, pulvinocortical projections convey mismatches between self-induced running speed and observed optic flow [9]
Cholinergic	(-) The time for basal forebrain neurons to respond to stimuli (in monkeys) [28] and elicit modulation in V1 (in mice) [15] is too slow to contribute transiently to fast stimulus-context effects (+) In humans, ACh reduces spatial spread of BOLD activity in V1 [25] as well as perceptual surround suppression effects [26] (+) Ionophoretically applied ACh reduces spatial summation in primate V1 [27]	(+) Blocking muscarinic ACh receptors reduces attentional effects in primate V1 [33]	(+) Using neural mass models of laminar activity, it was shown that cholinergic input enhances the activity of superficial pyramidal neurons, which might code the precision of prediction errors in PP [80] (-) The latency of basal forebrain neurons in responding to stimuli (in monkeys) [28] and eliciting modulation in V1 (in mice) [15] may be too long to contribute to PP

^aKey: (+), evidence in favor of a match between the specified type of RP (row) and a function (column); (-), evidence against this combination.

the gain of feedforward activity from the LGN to V1 through reciprocal connections with the reticular thalamic nucleus [41]. Further research is necessary to precisely pinpoint this mechanism.

Given the relatively slow timescale of high-level information feedback effects in V1 (in primates latencies ranging from 118 to 235 ms have been described), cholinergic projections may be fast enough to contribute to high-level RP in V1. ACh has been shown to facilitate attention-related activity through muscarinic receptors in macaque V1 [33].

In summary, feedback of high-level information depends on corticocortical projections to the primary sensory cortex, but also depends on pulvinar activity which affects the primary sensory cortex directly or indirectly. Modulation of the visual cortex by high-level information is likely to be facilitated by cholinergic projections. Additional pathways could play a role in transferring high-level information to V1, such as direct projections from the amygdala to V1 [42] conveying emotional significance. Furthermore, reward value effects may be mediated by long-lasting synaptic changes rather than by acute feedback from higher cortical areas [30,36].

Predictive Processing

The foundations of predictive coding can be traced to Helmholtz's ideas on perceptual inference [43]. Although several theoretical predictive coding models have been developed [44–46], the term predictive coding is often associated with generative neural network models of visual information processing presented in [44]. Following [47], we use the term PP to refer to the general idea of learning and inferring from **generative models** in the brain.

PP is founded on the idea that the brain infers latent (i.e., not directly observable) causes of the sensory input patterns it receives; for example, the frequency components constituting a musical tone. PP postulates that the brain minimizes the transmission of redundant information by having a higher-level area predict the expected sensory input and transmit this prediction to a lower-level area, which then computes the error between the actual and predicted inputs. A higher region (e.g., V2) uses feedback pathways to convey predictions about the causal representations inferred in a lower cortical region (e.g., V1). The lower region (V1) computes a prediction error and transmits this to the higher area through feedforward connections (from V1 to V2). This motif is repeated throughout the information-processing hierarchy and every region in the hierarchy receives prediction errors through feedforward connections (from a lower region like the LGN) and top-down predictions (from a higher region like V2) [44,48]. This information is used to infer causal representations that reconcile the representation at a lower level with the top-down prediction. However, this general scheme leaves open how exactly interareal and interlaminar connections in the neocortex may support PP (Box 2). The causal representations inferred in different regions vary in complexity, with higher levels inferring causes that are more integrative (temporally and/or spatially) than the causes inferred at lower levels, which are more concerned with sensory details. For example, neurons in lower regions exhibit selectivity for edge orientation and process information across smaller timescales [49,50] whereas higher regions are selective to more integrated sets of features like faces [51] and process information over longer timescales [49,50].

Evidence for PP has been found in rodents [52,53], humans (Box 3), and nonhuman primates [54]. In a study [52], using two-photon imaging in a virtual-reality apparatus for mice, the authors argued that the projections from the A24b/secondary motor cortex (M2) to V1 convey a body-movement-based prediction of visual flow. Using a similar experimental setup, it was found that excitatory neurons in layer 2/3 of the mouse V1 respond to mismatch between actual and predicted visual feedback [53]. Evidence for hierarchical predictions comes from studies in the face-processing area [55] of monkeys, which learnt to identify sequences comprising a 'predictor' face stimulus followed by a 'successor' face stimulus [54]. Comparing neural responses to a given successor in a learned versus a violation sequence showed that the middle lateral (ML) area emitted prediction errors relative to the expected successor. These errors were lower when the predictor was a mirror-symmetric view of the learned predictor. This suggests that the ML area receives top-down predictions from the anterior lateral area, which is recurrently connected to the ML and exhibits mirror-symmetric tuning [56].

What requirements does PP represent and which feedback projections can fulfill these requirements? To compute prediction errors reliably, receptive fields of neurons in a higher-level region that generate predictions need to be aligned, to some degree, with the receptive fields of neurons in a lower-level region. In mice, both corticocortical (from LM) and pulvinocortical (from LP) projections fulfill this criterion and could therefore contribute to PP [9,23]. For instance, a LM neuron sends feedback to V1 neurons having receptive fields flanking its receptive field orthogonal to the direction of its preferred orientation [56]. This orthogonality suggests that LM output may suppress predictive representations in V1. Although pulvinar projections to V1 exhibit weak orientation tuning, its connectivity with the cortex has a very organized structure. For every direct corticocortical pathway in humans, monkeys, and mice, the pulvinar provides an indirect corticothalamocortical pathway [8,40,57,58]. This indicates that the pulvinar might play a significant role in PP (Box 4), similar to its role proposed for attention [39].

Box 2. Cortical Microcircuit for PP

Inspired by previous diagrams [3,66,92–94], we propose a pattern of cortical connectivity that supports PP (Figure I). This framework proposes a neuroanatomical implementation for previously discussed models of predictive coding (e.g., [48]). We note that Figure I shows only circuitry involved in PP and ignores other known anatomical connections (e.g., feedback projections to infragranular layers, intra-areal efferents from supragranular to infragranular layers).

In Figure I, circles denote neuronal populations coding a particular signal in PP. Gray broken vertical and horizontal lines denote different cortical areas and neocortical layers, respectively. Black and colored arrows represent intra-areal and interareal connectivity, respectively. Broken-line arrows denote cell-level one-to-one projections relaying signals computed in one area to another area (this relaying may not be necessary; see below for explanations) and unbroken-line arrows denote many-to-many connectivity. $r^{(i)}$ denotes the representation of a cause of sensory input inferred in area i . It captures both structural and temporal dynamics in the sensory input. $e^{(i-1)}$ denotes error in the prediction of $r^{(i-1)}$.

Feedforward connections, originating mostly in superficial layers and targeting granular layer 4 [2], transmit prediction errors in this microcircuit (broken blue arrows). Thus, prediction errors are coded by two distinct populations. At a cellular level, this can be achieved by a single population that sends efferents to populations coding $r^{(i+1)}$ and local projections to populations coding $r^{(i)}$. In mice, L2/3 pyramidal neurons having axonal morphologies with these properties have been reported in the primary somatosensory barrel cortex [95].

Cortical feedback projections are less strictly organized. They prominently originate in infragranular layers and avoid the granular layer [96]. These projections transmit top-down predictions computed by nonlinear transformation of representations in a higher-level region (unbroken green arrows). The circuitry within an area entails convergence of prediction errors [from area $(i-1)$] and top-down predictions [from area $(i+1)$] to infer representations [$r^{(i)}$]. The most prominent intra-areal excitatory projections are from layer 4 to layer 2/3 and from layer 2/3 to layer 5 [97]. This indicates that incoming information converges in the supragranular layers, from where representations are relayed to infragranular layers for transmission to lower-level areas. L5 pyramidal neurons that project locally to supragranular layers and those having extrinsic projections have been observed in the mouse V1 [98]. An interconnected population in L5 comprising these two cell types will avert having to replicate representations in the supragranular and infragranular layers of a given area.

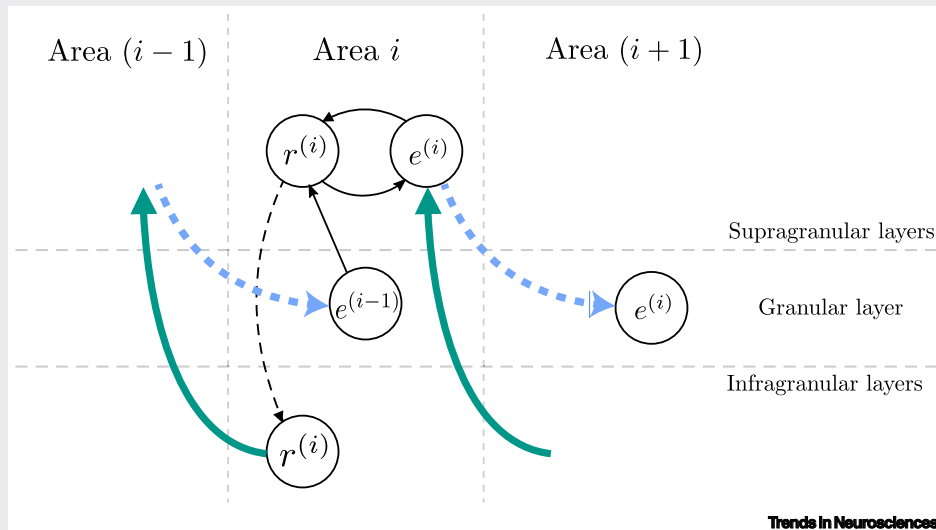


Figure I. Mapping of a Predictive Processing Model onto Interareal and Intra-areal Cortical Connectivity.

Regarding neuromodulators, there is little evidence on their involvement in PP. Using pharmacological manipulations of cholinergic transmission, it was argued that ACh may modulate the gain of neurons that encode prediction errors in V1 superficial layers [59]. However, more definitive evidence for this idea remains to be obtained.

In conclusion, these results suggest an involvement of corticocortical and pulvinocortical RP in PP, whereas further studies are needed to examine the role of neuromodulators in PP.

Box 3. RP in Human V1

Brain imaging using fMRI combined with transcranial magnetic stimulation (TMS) provides insights into RP in the human visual system. Recent fMRI evidence shows that top-down influences are task related, predictive, and related to predictions of spatiotemporal features. For example, cortical feedback contextualizes feedforward input [99] and predicts the representation of moving stimuli in V1 in time [100–102]. The neuronal representations of motion stimuli in V1 vary depending on whether an expectation is fulfilled or violated [100,103–105], and these expectation-related signals are updated fast enough to project to new, post-saccadic retinotopic locations after eye movements [101]. TMS stimulation in cortical area V5 50 ms prior to stimulus onset interrupts the processing of motion predictions in V1, showing a causal influence of top-down predictions on visual perception [106]. Top-down contextual effects in V1 lead to insertions of illusory contours [107] and to changes in the estimated point of disappearance of a flash [108]. Top-down predictions not only extrapolate the stimulus context but even construct new visual features (i.e., for visual illusions) and trigger the recall of remembered patterns with high temporal precision [101,109]. The complex interplay between stimulus expectation and confirmation of stimulus appearance can tune internal models over time [102] and the information of those internal models that we are conscious of helps us expand predictions over time [78] and space [79]. One way to conceptualize these processes is that cortical feedback to superficial layers of V1 provides a kind of ‘mental line drawing’ of the expected information [110] (Figure I). These mental line drawings can be of fine brushstrokes (high spatial frequency) or rough brushstrokes (low spatial frequency) [111,112].

However, top-down predictions can also be categorical and liberated from precise spatiotemporal appearance: like a blackboard can be used to sketch ideas, V1 receives content from peripheral coordinates and places it in foveal coordinates for cognitive comparison [113]. The ability to compare two stimuli in one’s mind declines if TMS interferes with the feedback of activity to foveal parts of V1 [114]. In another example of abstract prediction projected to V1, the instruction to imagine a sound of birds [115] leads to categorical activation in V1 [78,116] not necessarily related to a concrete visual instance of a bird. RP in V1 can therefore predict abstract categorical concepts as well as concrete features.

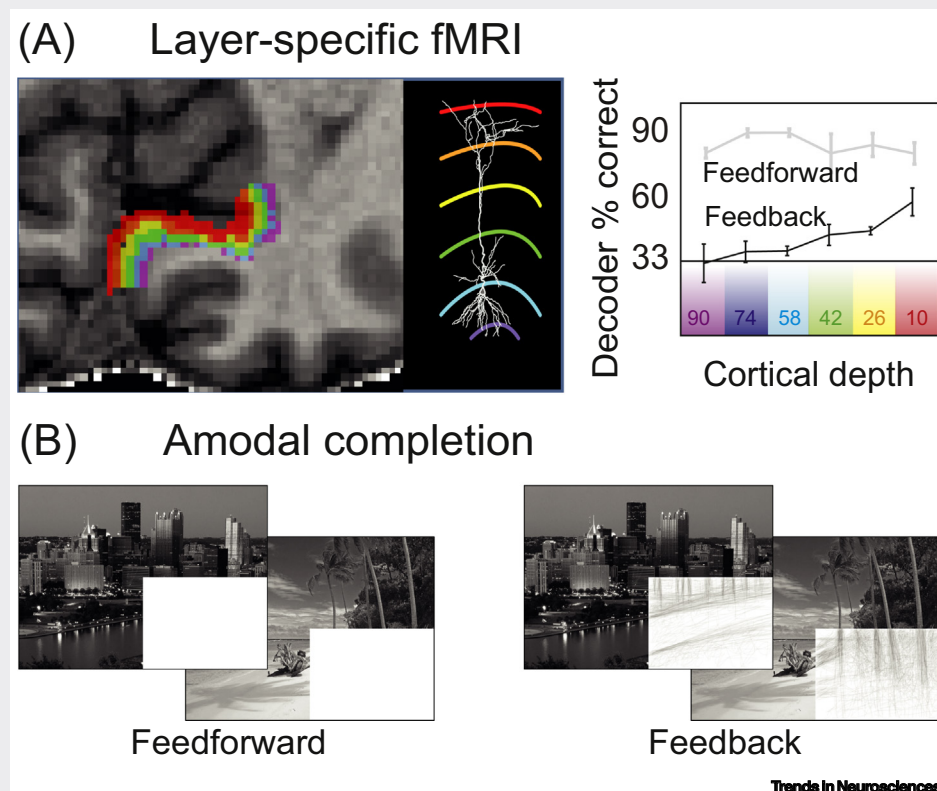


Figure I. Recurrent Processing in Human V1. (A) High-resolution fMRI can discriminate between different cortical depths (left panel). The superficial layers of V1 (red and orange; 10–26% of cortical depth) receive top-down feedback from other parts of the brain. Brain decoders detect patterns of activity and use them to guess which image of three possible images is presented (feedforward) or which of three possible images is occluded by the white rectangle [based on top-down feedback; see (B) for example images]. Note that the chance level is 33%. (B) Top-down cortical feedback helps to predict occluded information in an image – in much the same way as subjects are able to fill in the empty space with line drawings. Adapted from [110].

Box 4. Proposed Role of the Pulvinar in PP

We propose that the pulvinar provides an indirect pathway for transcortical communication between cortical areas involved in PP. Information propagates from lower to higher areas by continuous exchange of predictions and errors between adjacent areas in this hierarchy. The pulvinar may facilitate this process by providing an indirect pathway for communication between nonadjacent areas in this hierarchy (Figure I). This allows simultaneous exchange of predictions (denoted by 'P') and errors (denoted by 'E') directly between higher and lower areas. Moreover, it enables relaying of predictions from a higher area to a lower area without a reciprocal transmission of errors. In Figure I, the pathway that transmits errors via the pulvinar is shown in a dash-dot-dash pattern to distinguish between these two types of error reporting. Computationally, such indirect pathways are similar to 'skip connections' [117] that are often used in neural network models designed for real-world tasks.

The presence of topographically organized corticothalamic connections in the pulvinar [8,40,57] is proposed to support its ability to flexibly route information between different cortical regions in PP. This provides a pathway for indirect transcortical communication via subregions in the pulvinar where corticothalamic projections from different cortical areas overlap. Furthermore, the corticothalamic connections within the pulvinar are organized according to the topographical organization of the cortical areas themselves [8], which will enable the pulvinar to simultaneously coordinate communication between different cortical areas. This could also explain the presence of mismatch signals in the pulvinar that correspond to a comparison between fundamentally different quantities, as is the case, for instance, when comparing visual flow, arising from sensory input, and running speed, a motor signal [9]. The proposed scheme relates to PP and does not exclude other functions of the pulvinar (e.g., stimulus-context modulation, high-level feedback).

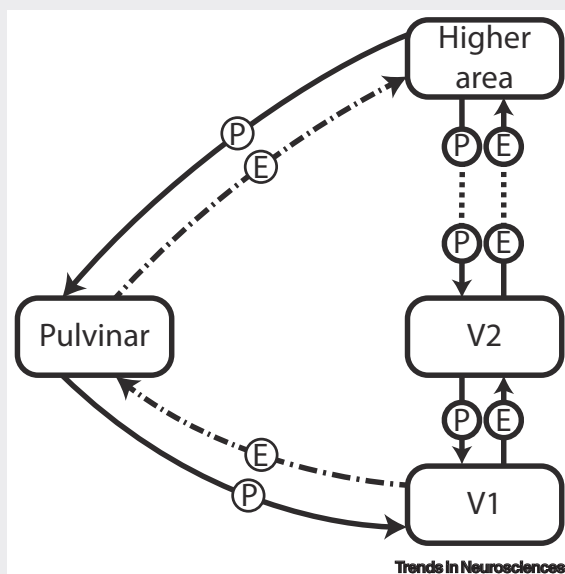


Figure I. Corticopulvinar and Pulvinocortical Connections as a Short Cut for Predictive Processing.

Capturing Three Functions Under an Overarching Concept?

So far, our review of experimental findings and models suggests that RP is a diverse phenomenon that is likely to subserve multiple functions through anatomically distinct pathways. However, this general observation leaves open the question of whether this variety of functions may be captured under a single overarching concept. At this stage of investigation, it is clear that definitive answers to this question cannot be articulated yet, but current evidence allows us to formulate empirically and theoretically grounded hypotheses.

A first hypothesis addresses whether stimulus-context modulation can be functionally subsumed under PP. Computational modeling studies have suggested that phenomena such as surround suppression can be explained by PP schemes [44]. They conceptualized superficial neurons in V1 as encoding errors in the predictions received from a higher-level region. These neurons

responded strongly to an oriented bar within the receptive field of a V1 cell and weakly to a bar extending into the extrareceptive field (the surround region; ‘end stopping’). This was attributed to the natural image statistics learned by the higher-level region generating the prediction. For instance, a naturalistic linear stimulus in a neuron’s receptive field usually extends into neighboring regions rather than occurring in isolation. In that case, the actual sensory input is cancelled by the prediction. In a PP model incorporating competitive biases, Spratling [60] showed that other properties of V1 neurons, such as orientation selectivity, spatial and temporal frequency tuning, and size tuning, could also be reproduced. Similarly, figure-ground segregation can be conceptualized as resulting from PP, wherein previously learned principles such as contour continuity are used to construct an inferential representation of the figure explaining the sensory input. Moreover, PP has been argued to explain several other phenomena, such as repetition suppression and mismatch negativity (MMN) responses [61]. It can be applied to domains other than vision, such as the representation of internal-body parameters [62], hearing, and other sensory modalities [63,64]. Whereas the original computational models focused on two-layer networks [44,45], PP can be used to train multilayer neural networks in an unsupervised manner using a neurobiologically plausible learning rule [48]. Thus, PP constitutes a powerful computational framework holding promise to explain a wide variety of observations involving sensory processing, learning, and perception. Moreover, when a high-level representation in a trained multilayer predictive coding network is activated, it is able to regenerate the corresponding input pattern, which may help to explain properties of imagery [65].

Having said this, we should point out some potential limitations of PP as a framework attempting to explain the functions of RP in sensory, perceptual, and cognitive processing. First, PP constitutes a computational framework that leaves open crucial outstanding empirical questions; for instance, how spatially precise feedback modulation can be achieved. Second, the precise functional roles of the higher areas in sensory cortical hierarchies remain to be elucidated. Friston’s group [66] and others [67] have proposed a hierarchical Bayesian scheme in which the higher areas provide supraordinate priors to support predictions of sensory patterns at lower levels (high-level priors may pertain, for instance, to stimulus context or abstract scene information [67]). However, the concept of PP as a basic computational–representational motif is distinct from Bayesian inference, which focuses on computing posterior probability as an end goal that drives optimal decision making [68]. Moreover, the neural substrates coding Bayesian priors remain to be elucidated and may also be localized in lower or intermediate visual areas or in lateral cortical connectivity. Furthermore, a comprehensive theoretical framework should also encompass feedback of high-level information to lower areas (e.g., on the motivational value of stimuli, their semantic meaning, spatiotemporal context, top-down attentional salience, working memory [63]). This constraint applies because the current evidence implies that more information reaches back into the lower visual cortices than that purely required to infer visual objects’ properties. Thus, compatible with the PP framework in a broader sense, we propose to use the terms ‘interpretation’ and ‘inference’ to capture the functional diversity of neural feedback. These terms can be more generally applied to different kinds of cognitive, subjective properties attributed to causes of sensory inputs. Moreover, interpretation is a concept applicable in both spatial and cognitive domains and thus avoids the inherent connotation of prediction with ‘time’. In addition to coding how an object appears to us (perceptual interpretation), this concept includes what the object is (semantic interpretation) and the object’s ‘where’ and ‘when’ (spatiotemporal context) as well as its motivational value (behavioral significance).

RP and Consciousness

Finally, corticocortical RP has been associated with perception or, in other words, conscious sensory processing of external stimuli [69,70]. Pulvinocortical RP may also contribute to

perception as pulvinar activity reflects perceptual awareness of visual stimuli [71]. In addition to evidence raised in humans and primates, Petersen's group [72] showed that optogenetic suppression of RP-related activity in the mouse primary somatosensory cortex (S1) blocks perceptual detection, confirming the causal relevance of S1 responses resulting from RP. The consistency of these cross-species findings stands in contrast to the difficulty in addressing why RP may be causally important for conscious processing. We have previously argued that conscious processing arises to construct a multimodal, situational survey of the agent's surrounding world (including its own body), which subserves complex, goal-directed decision making and model-based learning [73] (cf. [74,75]). In generating this survey, it is necessary to integrate information streams arising in multiple sensory modalities, but also to integrate high-level information with low-level sensory representations. For instance, semantic meaning (presumably coded in temporal lobe areas such as the hippocampal formation and the anteromedial temporal lobe [76,77]) needs to be coupled to a specific sensory representation to generate the representation of a meaningful object that can be acted on [63]. Moreover, whereas some high-level information such as object identity or emotional significance typically lacks spatial selectivity, a coupling of this information to topographically precise sensory representations in lower sensory areas is required to perceive an interpreted object in precise spatial detail and context. Thus, in relation to consciousness, RP is proposed to associate high-level information with sensory-detailed representations, such that both can contribute to an interpreted situational survey. The initial wave of RP may be followed up by further bottom-up/top-down iterations, leading to subsequent refinements in perceptual interpretation. Again, the PP framework may offer a fruitful starting point for a computational modeling approach to this problem, although we note that many sensory predictions can be performed nonconsciously [78] and that the domain of conscious processing may be best delimited by investigating spatiotemporally 'wide' inferential representations [79].

Concluding Remarks

We have highlighted three forms of feedback to V1 and their involvement in three proposed functions of RP: stimulus-context modulation, high-level information processing, and PP. We propose that corticocortical projections are associated with all three functions. Cholinergic projections contribute to slow modulations of V1 activity. The pulvinar may not be able to convey specific visual features but may act as a shortcut in transferring predictions and errors between nonadjacent areas in the visual cortex. Future research should address the causal relevance of these various feedback routes in the light of their three proposed functions (see Outstanding Questions).

We postulate that PP, when taken to its full breadth, can encompass stimulus-context modulation and high-level information processing, providing a means to interpret sensory inputs in general. This leads to future directions in modeling: most existing PP models have focused on corticocortical feedback, but now the inclusion of pulvinar and neuromodulatory projections in these models will help to bridge the gap between neurobiological and computational studies. PP models can become more comprehensive by incorporating different functions of RP, which can improve our understanding of perception as a process by which internal modeling of singular causes is integrated with high-level information and spatiotemporal context.

Acknowledgments

This project has received funding from the EU's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement (SGA2) 785907 Human Brain Project (C.M.A.P. and L.M.). We thank Dr Lucy S. Petro, three anonymous reviewers, and the editor for their insightful comments.

Outstanding Questions

Several predictive processing models of vision assume that feedback is spatially specific. How spatially precise do the receptive fields of the feedback source have to be to achieve a functionally effective form of predictive processing? In addition, how is spatially precise modulation in V1 achieved given that receptive fields in higher cortical regions are much larger?

Stimulus-context modulation, feedback of high-level information, and predictive processing affect perception. Is the modulation of V1 activity that arises through recurrent activity causally related to these effects on perception?

Do cholinergic projections play a causal role in stimulus-context modulation, feedback of high-level information, and predictive processing? If they do, through which neural mechanisms?

Which subtypes of neurons, distributed across cortical layers, fulfill distinct functions in predictive processing?

Given the empirical evidence for error coding in superficial cortical laminae, how, and at which anatomical loci, are representations of causes precisely coded [r^0 in Box 2]?

Do cortical feedforward and feedback circuits implement a form of Bayesian inference for perception or are the computational motifs of predictive processing used in other ways for constructing representations of causes of sensory input?

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